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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Anthony J. Cutie, et al.
Serial No.	:	09/702,263
Filed	:	October 31, 2000
For	:	**A CORE FORMULATION**
Group Art Unit	:	1616
Examiner	:	Robert M. DeWitty

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Jerome Rosenstock, Registration No. 25,456
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TRANSMITTAL OF APPELLANTS' APPEAL BRIEF

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Sir:

Transmitted herewith **in triplicate** is Appellants' Appeal Brief in support of their appeal in the above-identified application

A check in the amount of $320.00 is attached in payment of the required fee set forth in 37 CFR Section 1.17(c).

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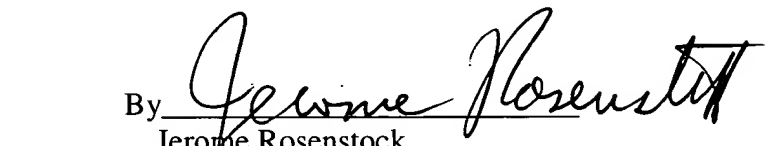
Respectfully submitted,

FROMMER LAWRENCE & HAUG, LLP
Attorneys for Applicants

By 
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Appellants' Docket
540541-2013.1

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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APPEAL BRIEF

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STATUTES

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Board of Patent Appeals and Interferences
Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

APPEAL BRIEF UNDER 37 CFR 1.192

Pursuant to the Notice of Appeal filed on July 29, 2002, in the above-captioned application, Appellants hereby appeal the final rejection dated (mailed) May 30, 2002 of claims 1 through 17, of the subject application and submits Appellants brief on appeal.

The brief is submitted in triplicate and contains the following sections:

1. REAL PARTY IN INTEREST;
2. RELATED APPEALS AND INTERFERENCES;
3. STATUS OF THE CLAIMS;
4. STATUS OF THE AMENDMENTS
5. SUMMARY OF THE INVENTION;
6. ISSUES;
7. GROUPING OF THE CLAIMS;
8. ARGUMENTS
9. CONCLUSION; AND
10. APPENDIX

1. REAL PARTY IN INTEREST

The real party in interest of the subject application is Aeropharm Technology Incorporated.

2. RELATED APPEALS AND INTERFERENCES

There are no pending appeals of applications or interferences of applications or patents related to the subject application.

3. STATUS OF THE CLAIMS

The status of the claims of the subject application is as follows:

Claims 1 through 17 were presented for examination in the subject application. Claims 1-17 were not amended during prosecution of the subject application. Claims 1 through 17, were finally rejected under 35 U.S.C. § 103(a).

The rejection of claims 1 through 17 is being appealed.

4. STATUS OF AMENDMENTS

No amendments to claims 1 through 17 were made.

5. SUMMARY OF THE INVENTION

The invention, as defined by the claims involved in this appeal, is summarized on page 1, bridging paragraph to page 2, line 8; page 2, last line to page3, last line and page 4, of the specification of the application in issue. The invention so defined relates to a core formulation which comprises a first **layer** comprising pioglitazone hydrochloride and a **core**, of a biguanide active ingredient, at least a portion thereof is **enclosed** by the first layer.

6. ISSUES

The first issue in this appeal is whether appealed claims 1-17 are unpatentable under 35 U.S.C. § 103(a) as being obvious in view of a first reference ("WHITCOMB"; hereafter defined)

and in view of a second reference ("RIEVELEY"; hereinafter defined). However, in deciding the first issue a second issue has been raised, namely, whether a formulation, of a layer of a first material partially enclosing a core of a second material, is formed when the materials in particulate form are mixed together.

7. GROUPING OF THE CLAIMS

Appealed claims 1 through 9 and 16-17 stand or fall together. Claims 10 and 11 stand or fall together. Claims 12 and 14 stand or fall together. Claims 13 and 15 stand or fall together.

8. APPELLANT'S ARGUMENT-THE FINAL REJECTION IS ERRONEOUS AND SHOULD BE REVERSED

A. APPELLANT'S CLAIMS ARE NOT RENDERED OBVIOUS IN VIEW OF THE PRIOR ART RELIED UPON BY THE EXAMINER

Appellants' invention as defined in Claim 1 through 17 are directed to (a) a formulation; (b) a method of administering a drug; (c) a method for producing a controlled release formulation; (d) a method of producing a combined medicament formulation; (e) a method of treating diabetes mellitus; and (f) pharmaceutical formulations. Claims 1-9 and 16-17 have the common limitation of a pioglitazone hydrochloride layer and a biguanide, e.g., metformin, core. Whereas the remaining claims are limited by particular combinations of medicaments.

Appealed claims 1-6 and 9-17 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Whitcomb, U.S. Patent No. 6,011,049 ("WHITCOMB"). It is submitted that Appellants' invention is not obvious in view of WHITCOMB and, accordingly the final rejection of these appealed claims should be reversed.

With respect to claims 1-9 and 16-17, certainly WHITCOMB reveals actually combining troglitazone (not pioglitazone) plus metformin. However, WHITCOMB does not reveal the

novel and patentable delivery system as defined by Appellants in claims 1-6 and 9 and 16-17. All that WHITCOMB reveals are conventional delivery systems, e.g., tablets, capsules, etc. In this regard, reference is made to WHITCOMB at col. 4, lines 35-41, where it is stated,

> The compounds can be employed individually, or can be combined in a single formulation, for example as a tablet, capsule, syrup, solution, as well as controlled release formulations. In a preferred embodiment, the sulfonylurea biguanide and glitazone are **formulated individually** and administered in the same manner that each is **normally used** clinically. (emphasis added);

and at Col. 5, lines 28-33, where it is stated:

> The compositions will normally be made for oral administration, for instance as tablets or capsules, but also may be in the form of aqueous suspensions or solutions, suppositories, slow release forms, for example employing an osmotic pump, skin patch, or the like.

What was not appreciated by WHITCOMB was the critical considerations involved in the subject invention, namely, a consideration of the relative concentrations of each drug, the dose requirement of pioglitazone vis-a-vis metformin, and the comparative solubility rates and absorption rates of each drug. In this regard, reference is made to the subject specification, at page 3, first through fourth full paragraphs, and in particular, the first full paragraph, where it is stated:

> ... The first layer [of the defined **core** formulation] should comprise pioglitazone hydrochloride because its dose requirement is lower compared to metformin. Additionally, it is slightly non-polar, its solubility rate slower, and its absorption rate thus dependent on its dissolution rate in the contents of the gastrointestinal tract compared with metformin.

WHITCOMB does not reveal or hint at the unitary core formulation as defined by Appellants.

Merely admixing two or three medicaments, as disclosed in WHITCOMB, does not address the considerations which Appellants' core formulation and method using such formulation addresses.

One of ordinary skill in the art in viewing WHITCOMB would understand and appreciate that WHITCOMB is only revealing a conventional "combination therapy", which involves administering two or more drugs separately. Combination therapy does not involve a mixture of two or more drugs and certainly not the core formulation as defined by Appellants.

Reference in this regard is made to WHITCOMB, at Figure 8 ("combination therapy"); Figure 11 ("combination therapy"); Figure 12 (... "Combination Therapy"); col. 1, lines 33-34 ("It has now been discovered that **combination therapy** ..." (emphasis added); col. 2, lines 6-26 ("FIG. 8 ... metformin and troglitazone **combination therapy**" ... FIG. 11 ...metformin ... troglitazone ... of **combination therapy** ... FIG. 12 ... metformin and troglitazone ... **combination therapy** ... (emphasis added)); col. 4, lines 38-41 ("In a prĕferred embodiment, the sulfonylurea, biguanide, and glitazone are formulated **individually** and administered in the same manner that each is **normally used clinically**." (emphasis added)); col. 6, lines 6-13 ("Overview ... troglitazone/glyburide **combination therapy** ... Patients treated with **combination therapy** ... (emphasis added)); col. 6, lines 53-54 ("... A greater number of patients treated with troglitazone **combination therapy** ... (emphasis added)); col. 11, lines 2-3 (" ... **combination therapy** of troglitazone and sulfonylurea appears to be safe ..." (emphasis added)); col. 11, lines 15-17 ("CONCLUSIONS Troglitazone/glyburide **combination therapy** is well tolerated ..." (emphasis added)); and col. 15, lines 21-24 ("After the initial ... period ... the remaining subjects were dosed with a combinatin of metformin and troglitazone (1000 mg metformin **BID**, 400 mg troglitazone **QD** ..." (emphasis added)).

One of ordinary skill in the art would not be led to Appellants' core formulation from a view of WHITCOMB.

The Examiner has stated,

> The combined ... may take the form of a tablet. One would know that in the formation of the tablet, the ingredients would be compressed together, thereby allowing a portion of metformin to be covered with pioglitazone, i.e., forming a core and a first layer.

Additionally, the Examiner has stated and maintained this position that:

> WHEREAS Whitcomb does not teach a first layer and a core covered by at least a portion of the first [layer], it is **understood** by the Examiner that in the combination of pioglitazone and metformin, portions of pioglitazone would cover metformin, (emphasis added).

Firstly, a question to be asked is **from what or whom** does the Examiner obtain his understanding? The Examiner has presented not a single authority to establish that such is true. Certainly, a core, at least a portion of which is enclosed by said first layer is not disclosed or hinted at by the *combination* of pioglitazone and metformin. *In re GPAC*, 57 F.3d 1573, 35 USPQ 2d 116 (Fed. Cir. 1995).

It is respectfully submitted that one of ordinary skill in the art would not know of this formulation. This is pure conjecture on the part of the Examiner without any support. As stated by the CCPA in *In re Way*, 514 F.2d 1057, 185 USPQ 580, 584 (CCPA 1973),

> There is no support for [the solicitor's] analogy from the technical literature and a fertile imagination does not make the claimed invention obvious.

Additionally, reference is made to *In re GPAC, supra* at 1123, where the CAFC stated:

> We believe that this statement by the Board in support of its rejection ... is conclusory and lacks the factual basis required to validate a claim rejection under Section 103. See In re Warner, 379 F.2d 1011, 1017, 154 USPQ 173, 178 (CCPA k1967) "A rejection based on Section 103 must rest on a factual basis, and these facts must be interpreted without hindsight reconstruction of the invention from the prior art... [The Board] may not ... resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in its factual basis") cert denied, 389 U.S. 1057df (1968).

Reference is also made to *Exparte Yamamoto*, 57 USPQ 2d 1382, 1383-84 (BPAI 2000).

Arguendo, it can just as easily be forwarded that (1) separate medicament layers are formed; or (2) a mixed active ingredient core is formed with a metformin layer covering it; or (3) a metformin core is formed with a pioglitazone layer; or (4) a mixture of different discrete cores, are formed, etc. But, what is realistic?

Of course, one of ordinary skill in the art knows the difference between a coated particle and a core (the central, foundational part of a body or unit) having a layer thereon.

Secondly, nowhere in WHITCOMB is an **actual** combination of pioglitazone and metformin described. Accordingly, in this regard, certainly the Examiner's "understanding" could not have come from conjecture?

A "core" is defined in "Webster's Third International Dictionary", (1993) (copy enclosed) as "the central and often fundamental part of a body, mass or construction as distinct from the enveloping part of a difference in nature or by being cut out or separated ..." A "layer" is defined in this dictionary as "a. one thickness, course or fold laid or lying over or under another ... b. stratum, bed ...". Accordingly, **arguendo** assuming that this fertile, imaginative

"understanding" is valid, the "combination" does not form particles which are a core of metformin i.e. a central part of a body, and the pioglitazone does not form a layer "laid or lying over" a portion of a core.

One of ordinary **skill** in the art would not consider or imagine mixed particles as being a core having a layer on a portion thereof. *In re Way, supra.*

It is submitted that claim 1-6, 9 and 16-17 are not rendered obvious under 35 U.S.C. § 103(a) in view of WHITCOMB and, accordingly, reversal of the rejection of these claims thereunder is requested.

With respect to claims 10 and 11, WHITCOMB, does not reveal a "combined" medicament formulation, but rather "combination therapy". In this regard reference is again made to WHITCOMB, at col. 1, lines 33-34; FIG. 8 (col. 4, lines 6-8); FIG. 12 (col. 4, lines 23-26); col. 6, line 13; col. 6, line 54; col. 9, line 8, col. 11, lines 2 and 16; and col. 13, line 10. As previously indicted, WHITCOMB does not *per se* reveal that pioglitazone hydrochloride is combined with metformin.

It is respectfully submitted that claims 10 and 11 are not rendered obvious under 35 U.S.C. § 103(a) in view of WHITCOMB.

Claims 12 and 14 are defined in terms of the combination (not combined therapy)of individual medicaments of pioglitazone hydrochloride combined with phenformin. The deficiencies of WHITCOMB, discussed above with respect to claims 10 and 11, are reiterated hereat. WHITCOMB does not reveal or even hint at the combined medicaments defined in claims 12 and 14. claims 12 and 14 are not rendered obvious under 35 U.S.C. § 103(a) in view of WHITCOMB.

Claims 13 and 15 are defined in terms of the combined medicaments of pioglitazone hydrochloride and buformin. The discussion, above, concerning claims 12 and 14 apply equally as well to claim 13 and 15, except for the specific medicament combination. Accordingly, claims 13 and 15 are not rendered obvious under 35 U.S.C. § 103(a) in view of WHITCOMB and reversal of the final rejection thereunder is requested.

With respect to the above discussion concerning claims 10-11, 12 and 14 and 13 and 15, it is to be pointed out that the Examiner has stated, "... Whitcomb teaches that the compounds can be combined in a single formulation as a tablet (col. 4, lines 35-37)." However, one can not just pick and choose from a reference to find obviousness. The reference must be looked at as a whole for what it teaches to one of ordinary skill in the art. *Bausch & Lomb v. Barnes – Hind/Hydrocurve*, 796 F.2d 443, 230 USPQ 416 (Fed. Cir. 1986). As the former Court of Customs and Patent Appeals held in *In re Wesslau*, 353 F.2d 238, 147 USPQ 391, 393 (CCPA 1965), cited in *Bausch, supra*, at 419,

> It is impermissible within the framework of Section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art.

In this regard, a single line in a prior art reference should not be taken out of context and relied upon with the benefit of hindsight to show obviousness. If one fully reads col. 4 lines 35-41, one of ordinary skill in the art is taught that WHITCOMB reveals treatment by combination therapy and not by a combined medicament therapy. In this regard, col. 4, lines 35-41 reveal the following:

> The compounds can be employed **individually**, or can be combined in a single formulation for example as a tablet ... In a preferred embodiment, the sulfonyl urea, biguanide, and glitazone are formulated **individually** and administered in the same manner that each is **normally** used clinically. (emphasis added).

Viewing this passage with the preceding and following teachings in the specification of WHITCOMB, e.g., col. 1, lines 33-34; FIG. 8; FIG. 12; col. 6, line 13, etc., discussed previously, one can not escape the conclusion that WHITCOMB is directed to combination therapy and not combined medicament therapy.

Claims 1-17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Rieveley, U.S. Patent No. 6,153,632. ("RIEVELEY"). Concerning claims 1-9 and 16-17, all that RIEVELEY reveals is a combination of a glitazone and a biguanide. RIEVELEY does not reveal the core formulation as defined by Appellants. All that RIEVELEY reveals are conventional delivery vehicles. In this regard, reference is made to RIEVELEY at col. 6, lines 41-61, where it is stated:

> The subject compositions ... can be administered parentally, topically or internally, but preferably orally ... The compositions ... may be formulated in any suitable orally acceptable form by employing **conventional** formulation techniques ... in pharmaceutically acceptable forms such as tablets or capsules in admixture ... carriers....may also be used in **combination** with other ... agents ... may be formulated in one unit ... or in separate units administered at the same time or at separate times ...administered in a single dosage form or in the form of subunits several times a day. (emphasis added).

The Examiner has stated:

> As above, Rieveley does not explicitly state the use of pioglitazone HCI in the first layer and a biguanide at the core ... but because there is **no evidence of criticality** in such Applicant's formulation, the instant invention is made obvious by Rieveley (emphasis added).

As shown, above, Appellants have shown a criticality. As with WHITCOMB, reference is made to the subject specification at page 3, first through fourth paragraphs, especially the first full paragraph. Again, merely combining or admixing two or three medicaments does not address the problems or considerations addressed by Appellants' invention as defined in claims 1-9 and 16-17.

Why would one of ordinary skill in the art be led to Appellants' invention as defined in claims 1-9 and 16-17 when RIEVELEY does not reveal or hint at a core formulation; (2) reveals only conventional delivery vehicles (RIEVELEY at col. 6, lines 41-61); and (3) does not appreciate the criticality considered in Appellants' inventive core (the subject specification at page 3, first through fourth full paragraphs, especially the fourth full paragraph).

It is respectfully submitted that claims 1-9 and 16-17 are not rendered obvious, under 35 U.S.C. § 103(a), in view of RIEVELEY. Reversal of the rejection of these claims thereunder is requested.

Concerning claims 10 and 11, RIEVELEY reveals a list of **ten (10)** insulin sensitizers one or more of which can be combined with one or more of (a) an injectable insulin, (b) a list of **six (6)** hypoglycaemics, (c) a list of **two (2)** biguanides, (d) a list of **three (3)** alphaglucosi dose inhibitors, and (e) a list of **twenty-six (26)** U.S. patents directed to orally administered insulins having at least **nine (9)** different classes of such compounds. RIEVELY does not specifically

reveal or hint at the combined medicaments defined in claims 10 and 11. One of ordinary skill in the art would have to pick and choose from a large number of combinations and permutations to arrive at the combination of claims 10 and 11 from a view of RIEVELEY. *E.I. DuPont de Nemours & Co. v. Ladd*, 140 U.S.P.Q. 297, 300-02 (C.A.D.C. 1964); *Bausch & Lomb, supra.*. It is submitted that claims 10 and 11 are not obvious under 35 U.S.C. § 103(a) from a view of RIEVELEY and, accordingly, the rejection thereunder should be reversed.

With respect to claims 12 and 14, again the discussion above, with respect to claims 10 and 11, apply equally as well. RIEVELEY does not reveal or hint at the combined medicaments of pioglitazone hydrochloride and phenformin and thus the rejection of these claims in view of RIEVELEY should be reversed.

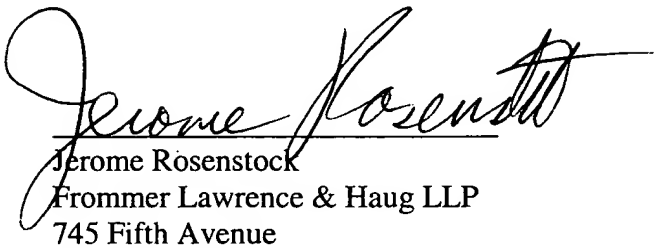
With respect to claims 13 and 15, the discussion with respect to claims 10 and 11 apply equally as well. RIEVELEY does not reveal or hint at pioglitazone hydrochloride combined with buformin and reversal of the rejection of claims 13 and 15 in view of RIEVELEY warrants reversal.

CONCLUSION

In summary, Appellants are claiming a novel, patentable formulation comprising a core of a first anti-diabetic agent having a layer of a second anti-diabetic agent enclosing at least a portion of the core. Additionally, Appellants claim novel, patentable formulations of "combined" anti-diabetic medicaments. Neither the unique core formulation nor the combined formulation are revealed or hinted at from the two principle references relied upon by the Examiner to support the rejection of the claims under 35 U.S.C. § 103(a). The Examiner has used his "fertile imagination" and "conjecture" to find the formulations obvious from a mere

mixing of different particles notwithstanding that the particles of the references actually employed are not those of the combined medicaments which are claimed.

It is respectfully submitted that the Examiner's final rejection of claims 1-17 under 35 U.S.C. § 103(a) should be reversed.



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APPENDIX

1. A core formulation comprising,

(a) a first layer comprising pioglitazone hydrochloride or a pharmaceutically acceptable salt thereof as active ingredient,

(b) a core, at least a portion of which is enclosed by said first layer, comprising a biguanide as active ingredient.

2. The formulation as defined in claim 1 wherein said biguanide is metformin.

3. The formulation as defined in claim 2 wherein said pioglitazone hydrochloride is present in an amount ranging from 1 mg to 45 mg and, said metformin is present in an amount ranging from 10 mg to 4000 mg.

4. The formulation as defined in claim 2 which further comprises a biodegradable shell having a predetermined rate of degradation covering at least a portion of said first layer to provide a predetermined delay in the time period of release of at least said pioglitazone hydrochloride.

5. The formulation as defined in claim 2, wherein said pioglitazone hydrochloride and/or said metformin are present as biodegradable microspheres having a biodegradable shell coating and where said shell coating has a predetermined rate of degradation.

6. A method of administering pioglitazone hydrochloride and metformin to a mammal, which comprises treating the mammal with the formulation defined in claim 2.

7. A method for producing a controlled release formulation, which comprises:

(a) producing a hollow outer shell comprising a biodegradable material having a predetermined rate of degradation to provide a predetermined delay in the time period of release of the contents destined to be enclosed by said shell;

(b) inserting a core comprising metformin and having an outer layer comprising pioglitazone hydrochloride partially enclosing said core, into said hollow outer shell; and

(c) sealing said core within said hollow outer shell.

8. A method of producing a combined formulation of pioglitazone hydrochloride and metformin, which comprises:

(a) forming a core of the metformin; and

(b) depositing a layer of pioglitazone hydrochloride on at least a portion of surface of said core.

9. A method of treating diabetes mellitus in a patient in need thereof, which comprises administering to the patient the formulation of claim 1 wherein said active ingredients are each present in an effective amount.

10. A pharmaceutical composition comprising an effective amount of pioglitazone hydrochloride combined with an effective amount of metformin.

11. A method of treating diabetes mellitus in a patient in need thereof, which comprises, administering to the patient the composition of claim 10.

12. A pharmaceutical composition comprising an effective amount of pioglitazone hydrochloride combined with an effective amount of phenformin.

13. A pharmaceutical composition comprising an effective amount of pioglitazone hydrochloride combined with an effective amount of buformin.

14. A method of treating diabetes mellitus in a patient in need thereof, which comprises, administering to the patient the composition of claim 12.

15. A method of treating diabetes mellitus in a patient in need thereof, which comprises, administering to the patient the composition of claim 13.

16. A method of treating diabetes mellitus in a patient in need thereof, which comprises, administering to the patient the composition of claim 1 wherein the biguanide is phenformin.

17. A method of treating diabetes mellitus in a patient in need thereof, which comprises, administering to the patient the composition of claim 1 wherein the biguanide is buformin.